REMARKS

Upon entry of this paper, claims 1, 2 and 4-36 are pending, of which claims 18 and 19 are withdrawn. Claim 3 was previously canceled. Claims 4, 5, 7, 8, 10-12, 14, 15, and 18 are hereby amended to further clarify that the composition is aqueous. Support for these amendments can be found throughout the specification, and in the claims as originally filed, including for example, in Examples 1-3 on pages 10-12 of the specification, and claim 1 as originally filed. Claim 18 is amended solely for antecedent basis correction. Thus, no new matter is introduced by these amendments. Applicants respectfully request reconsideration of the claims in view of the following remarks.

Information Disclosure Statement

As noted by the Examiner in the Office Action, a PTO-1449 form was inadvertently omitted ("the inadvertently omitted PTO-1449") when the Information Disclosure Statement was electronically submitted on July 20, 2011. The Examiner requests that Applicants re-submit the inadvertently omitted PTO-1449. Applicants respectfully submit that Applicants re-submitted the inadvertently omitted PTO-1449 on August 12, 2011, which is acknowledged by the Examiner.

Rejections under 35 U.S.C. § 103

A. Illum in view of Grebow

Claims 1-2, 4-9, 12, 14-17 and 20-36 stand rejected as allegedly obvious over U.S. Patent No. 6,387,917 to Illum (hereafter "Illum"), in view of U.S. Patent No. 5,026,825 to Grebow (hereafter "Grebow"). Applicants respectfully traverse the rejection.

To reject claims in an application under 35 U.S.C. §103(a) the Examiner must establish a *prima facie* case of obviousness. Using the Supreme Court's guidelines enunciated in *Graham v. John Deere,* 383 U.S. 1, 17 (1966), one determines "obviousness" as follows:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

In *KSR Int'l Co. v. Teleflex Inc.,* No. 04-1350 (U.S. April 30, 2007), the Supreme Court reaffirmed the *Graham* test, and indicated that although it should not be rigidly applied, a helpful insight into determining obviousness is to consider whether there is a teaching, suggestion or motivation in the prior art that would lead one of ordinary skill in the art to combine known elements of the prior art to arrive at the claimed invention. Importantly, the Court emphasized that a patent examiner's analysis under Section 103 should be made explicit in order to facilitate review.

Thus, to establish a *prima facie* case of obviousness, the Examiner has an obligation to construe the scope of the prior art, identify the differences between the claims and the prior art, and determine the level of skill in the pertinent art at the time of the invention. The Examiner must then provide an explicit, cogent reason based on the foregoing why it would be obvious to modify the prior art to arrive at the claimed invention. Applicants respectfully submit

that the Examiner does not fulfill the obligation required to establish a *prima facie* case of obviousness.

As acknowledged by the Examiner, Illum does not disclose or suggest an antimicrobial agent selected from benzalkonium chloride, disodium EDTA, or a combination thereof, as recited in independent claims 1, 21, and 26. *See* page 4 of the Office Action. The Examiner further relies on Grebow for purported disclosure of the claimed antimicrobial agent. Applicants respectfully submit thats an artisan of ordinary skill would not be motivated to incorporate the antimicrobial agents of Grebow into the morphine composition of Illum to provide a stable morphine composition as claimed.

Grebow does not disclose morphine, let alone a stable morphine composition. Grebow is limited to calcitonin. Morphine is a small molecule opiate analgesic, which is distinct from a large molecule polypeptide hormone calcitonin. Molecules with different molecular weights as active ingredients in pharmaceutical compositions often encounter different challenges. For example, Grebow recognizes that molecules with a larger molecular weight, *e.g.*, calcitonin, encounter absorption problems, but not molecules with a smaller molecular weight. *See* Col. 1, lines 35-46. Grebow is directed to solve the stability problems encountered by calcitonin through the use of Δ-aminolevulinic acid.

As previously established, while Illum itself does not disclose stability problems with its product, an artisan of ordinary skill would nevertheless be wary of incorporating additional elements into a morphine composition due to its stability problems in general. However, an artisan of ordinary skill would not be motivated to adopt a problem solution targeted to a large molecule, *e.g.*, calcitonin with a molecular weight of about 3454 Da, to solve a

problem encountered by a small molecule, *e.g.*, morphine with a molecular weight of about 303 Da. Even if there were motivation to apply the solution offered by Grebow to the composition of Illum aiming to improve the stability problem encountered by morphine, which Applicants do not concede, the artisan would have implemented Δ-aminolevulinic acid, rather than an antimicrobial agent. Grebow emphasizes the role of Δ-aminolevulinic acid in increasing the stability of calcitonin composition by inhibiting nasal mucosal peptidases, which reduces the degradation of calcitonin. *See* Col. 1, lines 47-59. All compositions of Grebow comprise Δ-aminolevulinic acid.

As acknowledged by the Examiner, Grebow only discloses benzalkonium chloride and disodium EDTA, as optional preservatives in some clacitonin compositions exemplified in Examples 8, and 11-14. Grebow does not provide disclosure of or motivation for modifying the morphine composition of Illum by adding an optional preservative in the calcitonin composition of Grebow. Even if there were motivation to do so, which Applicants do not concede, there would still be no reasonable expectation of success for achieving a surprisingly stable morphine composition of the claimed invention.

In addition, Applicants previously submitted that an artisan of ordinary skill has recognized the stability problem encountered by morphine formulation, *e.g.*, evidenced by FDA Recall # D-581-2101 of Embeda (morphine sulfate and naltrexone hydrocholoride, Extended Release capsules), http://www.fda.gov/Safety/Recalls/EnforcementReport (hereafter "the FDA Recall"). In response, the Examiner states that the FDA recall only serves to show that the recall of the morphine product is due to its stability problem. The Examiner contends that there is no evidence to show that the stability problem is a result of an antimicrobial agent.

Applicants respectfully submit that the FDA recall was submitted solely to evidence the awareness of stability problem encountered by a morphine composition for an artisan of ordinary skill. Indeed, if the FDA recall disclosed that the stability problem observed in the morphine composition was a result of an antimicrobial agent, as requested by the Examiner, an artisan of ordinary skill could have tried to add an antimicrobial agent to a morphine composition with the expectation of obtaining a more stable morphine composition. However, since no correlation of an antimicrobial agent and stability of a morphine composition is disclosed or suggested in the prior art, it would not be obvious for an artisan of ordinary skill to implement an antimicrobial agent to a morphine composition for achieving a surprisingly stable morphine composition of the claimed invention.

Furthermore, the Examiner alleges that Applicants have not provided any evidence directly linking the use of different antimicrobial agents result in the degradation of morphine. Applicants respectfully submit that such evidence is not required given that the Examiner has failed to first establish a *prima facie* case of obviousness, which as discussed above is based upon known stability problems encountered by morphine compositions in general, and the lack of specific agents in Illum intended to prevent the degradation of morphine. It is only upon establishing a *prima facie* case of obviousness when the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the prima facie case, such as the comparative data referenced above by the Examiner. *See*, MPEP § 2145, *citing*, *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990).

For at least the reasons discussed above, Applicants respectfully submit that claims 1-2, 4-9, 12, 14-17 and 20-36 would not have been obvious over Illum in view of

Grebow, alone or in combination. Accordingly, Applicants respectfully request the withdrawal of the instant rejections and reconsideration of the claims.

B. Illum in view of Grebow, further in view of Tulin

Claim 11 stands rejected as obvious over Illum, in view of Grebow, and further in view of U.S. Patent No. 5,508,282 issued to Tulin-Silver (hereafter "Tulin"). Tulin is cited by the Examiner only for its purported disclosure of ascorbic acid or sodium ascorbate. Applicants respectfully traverse the rejection.

Tulin is directed to a nasal spray composition and method for treating rhinosinusitis. The important components in the compositions of Tulin are Vitamin C and caffeine. *See* Col. 3, lines 26-29. Tulin does not disclose morphine, or any opiate analgesic. Tulin highlights the benefit of lacking irritation and undesirable side effects offered by the compositions. *See* Col. 2, lines 50-53, and Col. 3, lines 5-8. Tulin is not directed to solve any stability problems, let alone the stability problem encountered by a morphine composition. Even if one artisan of ordinary skill consulted Tulin, which Applicants do not concede, there still would have been no reasonable expectation of successfully incorporating the optional preservatives in Grebow's calcitonin composition with the morphine compositions of Illum to achieve a stable morphine composition. Therefore, Tulin does not cure the deficiencies of Illum and Grebow.

For at least the reasons discussed above, Applicants respectfully submit that claim 11 would not have been obvious over Illum in view of Grebow, and further in view of Tulin, alone or in combination. Accordingly, Applicants respectfully request the withdrawal of the instant rejection and reconsideration of claim 11.

C. Illum in view of Grebow, further in view of Santus

Claim 13 stands rejected as obvious over Illum, in view of Grebow, and further in view of U.S. Patent No. 6,333,044 issued to Santus (hereafter "Santus"). Santus is cited only for its purported disclosure of sodium benzoate. Applicants respectfully traverse the rejection.

Santus is directed to a therapeutic composition with analgesic and anti-inflammatory activity, comprising KETOROLAC® as an active ingredient. Santus is not directed to morphine, or any opiate analgesic. Indeed, Santus discloses that the KETOROLAC® composition provides considerably higher analgesic and anti-inflammatory activity than morphine. *See* Col. 1, lines 42-50. An artisan of ordinary skill would not consult Santus for a morphine composition. Even if the artisan consulted Santus, which Applicants do not concede, there still would have been no reasonable expectation of successfully incorporating the optional preservatives in Grebow's calcitonin composition with the morphine compositions of Illum to achieve a stable morphine composition. Therefore, Santus does not cure the deficiencies of Illum and Grebow.

For at least the reasons discussed above, Applicants respectfully submit that claim 14 would not have been obvious over Illum in view of Grebow, and further in view of Santus, alone or in combination. Accordingly, Applicants respectfully request the withdrawal of the instant rejection and reconsideration of claim 13.

CONCLUSION

On the basis of the foregoing Remarks, Applicants respectfully submit that the pending claims of the present application are allowable over the prior art of record. Entry of the

Amendments and Remarks submitted herewith and timely allowance of this application are respectfully requested.

As noted above, the amendments of the claims above is being made solely to expedite prosecution of the present application and does not constitute an acquiescence to any reference identified by the Examiner. For the reasons set forth above, Applicants respectfully submit that all pending claims define patentable subject matter over the cited art, either considered alone or in combination. In view of the foregoing, Applicants believe that the entire application is now in condition for allowance, early notice of which would be appreciated. Should the Examiner not agree, then a personal or telephonic interview is respectfully requested to discuss any remaining issues in an effort to expedite the allowance of this application. Furthermore, entry of the Amendments and Remarks submitted herewith will place this application in condition for appeal if deemed necessary.

Applicants believe no additional fees are due. However, if any fee is required in connection with this communication, or if any overpayment has been made, Applicants authorize the Commissioner to charge any additional fees and/or credit any overpayments associated with this paper to Baker Botts L.L.P. Deposit Account No. 02-4377, Ref. No. 077350.0136.

November 8, 2011
Date

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